REMARKS

A. Regarding the Amendments

No claims have been amended by the present amendment. It is respectfully submitted that the claims are allowable as submitted in the Amendment filed May 28, 2002. As pending, the claims are supported by the specification and the original claims. Thus, claims 15, 18-22 and 44-46 remain pending.

B. Rejection Under 35 U.S.C. §101

Claims 15, 18-22 and 44-46 have been rejected under 35 U.S.C. §101 as allegedly not supported by either a specific and substantial asserted utility or a well established utility. Applicants respectfully disagree.

Initially it is noted that the rejection of claims 15-16 and 18-22 under 35 U.S.C. §101 was withdrawn in Paper No. 13. While claim 16 is no longer pending, claims 15 and 18-22 remain pending in the present application. Claims 15, 18 and 21 were amended in Applicants' last response, Paper No. 14, though not amended significantly, and claims 19 and 22 were not amended at all. However, these claims are all again rejected under 35 U.S.C. §101, in addition to claim 44 and new claims 45 and 46. Applicants respectfully reassert the argument previously presented.

It is alleged in Paper No. 15 that the application does not disclose the biological role or significance of the GDF-12 protein and therefore the specification does not provide a specific substantial and credible utility. Additionally it is stated that GDF-12 is an "orphan protein" which has been isolated by its structural similarity to known proteins, but which has no known utility. Applicants respectfully disagree.

Claims 15 and 18-22 are directed to a method of detecting a liver cell sample and claims 44-46 are directed to a method of detecting expression of GDF-12 in the liver of a subject. In general, the methods utilize an anti-GDF-12 antibody to detect GDF-12 in a specimen obtained from the subject, and compare the amount of GDF-12 detected in the sample with an amount in a control specimen, wherein a difference in the sample as compared to control is indicative of a liver cell proliferative disorder (claims 15 and 18-22) and abnormal expression of GDF-12 (claims 44-46).

Applicants maintain that a method of detecting a cell proliferative disorder by determining an amount of a protein produced by cells involved in the disorder, including the disclosed method of detecting a liver cell proliferative disorder based on determining the amount of GDF-12, is a well established utility that is specific, substantial and credible. The utility is specific in that the specification discloses that GDF-12 is specifically expressed by liver cells and, therefore, provides a specific marker for liver cells (see, for example, Figure 1). The utility also is substantial in that there is a real world value in providing a means to determine whether an abnormal amount of liver cell proliferation is occurring in a subject, as can happen, for example, in a subject with a hepatoma or a hepatocarcinoma, or whether there is a disorder such as hepatitis, wherein damage to the liver is not repaired by liver cell proliferation. Furthermore, the utility is credible because one skilled in the art would believe, for example, that an increased level of liver cell proliferation would be associated with increased GDF-12 expression because more liver cells would be expected to produce more GDF-12.

By analogy, Applicants have previously pointed out that the levels of various proteins, including cyclin D1, PCNA, prothrombin, and others are known to correlate with the level of proliferation of cells producing these proteins and that the detection of such proteins has been used in diagnostic procedures. Further in this respect, Applicants have pointed out that the level of prostate-specific antigen (PSA) in the blood was well recognized as a diagnostic marker of a prostate cell proliferative disorder, even though the function of PSA was not known. Thus, even

where the function of a protein such as PSA was not known, it was recognized that the level of PSA was increased above normal in benign prostate hyperplasia and in prostate carcinoma, presumably due, at least in part, to the increased number of prostate cells associated with these conditions and, therefore, that the levels of PSA can be indicative of a prostate cell proliferative disorder. Applicants submit that, similarly, in the present case, one skilled in the art, viewing the specification and having knowledge of the art, would have known, for example, that increased levels of GDF-12 can be indicative of a liver cell proliferative disorder such as a hepatoma because GDF-12 is produced by liver cells and because increased levels of PSA, which is produced by prostate cells, is indicative of a prostate cell proliferative disorder.

As it has been shown that the increased levels of GDF-12 can be indicative of a liver cell proliferative disorder, it is respectfully submitted that GDF-12 is not an "orphan protein." GDF-12 is not used in the invention in the same manner as the compound in Brenner v. Manson cited by the Examiner. In that situation, the claimed compound was claimed as an anti-cancer compound, without a showing of its own anti-cancer activity, because of its structural similarity to known anti-cancer compounds. The present situation is distinguishable in that GDF-12 has been shown to be present in liver cells. The value of GDF-12 as a marker for liver cells and cell proliferation disorders in liver cells is has been shown by its presence. GDF-12 is claimed as a marker for liver cells because of its own presence in those cells, not because of the presence of another member of the GDF family with structural similarity to GDF-12.

Additionally, the Examiner alleges that the GDF-12 has an "as of yet undetermined function or biological significance." (Paper No., 15, page 3.) It is noted that it is known that GDF-12 is expressed in liver cells but not in ovary, muscle, testis, spleen, intestine, pancreas, seminal vesicle, kidney, brain, thymus, lung or heart, as is set forth in Example 2 and Figure 1 of the application. It is also known that expression of GDF-12 increases with increased liver cell production. This shows a biological significance. Additionally, claiming of GDF-12 does not

claim as large of "an area of scientific development," as stated by the Examiner, as the GDF-12 claimed is limited by the amino acid sequence of SEQ ID NO:12.

In summary, it is submitted that the use of an antibody to determine the level of a protein, wherein the level of the protein is diagnostic of the proliferative state of cells that produce the protein, is a well established utility, which is specific, substantial and credible, and that, in view of the subject application and of knowledge in the art such as the use of PSA levels as indicative of a prostate cell proliferative disorder, one skilled in the art clearly would have recognized that an anti-GDF-12 antibody can be used to determine levels of GDF-12, which can be indicative of a liver cell proliferative disorder. Accordingly, it is respectfully requested that the rejection of the claims under 35 U.S.C. § 101 be removed.

C. Rejection Under 35 U.S.C. § 112

Applicants respectfully traverse the rejection of claims 15, 18-22 and 44-46 under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to use the invention and that the invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the rejection under 35 U.S.C. §101. Applicants respectfully disagree.

As set forth above, GDF-12 has the biological significance of increased expression with increased liver cell production. It is set forth that expression of GDF-12 is specific to liver cells. Additionally, the GDF-12 claimed is limited by the requirement that the polypeptide have an amino acid sequence as set forth in SEQ ID NO:12. As GDF-12 is shown to have both structural and functional characteristics, and one of skill in the art would have been able to practice the invention at the time of filing, it is respectfully submitted that claims 15, 18-22 and 44-46 meet the requirements of 35 U.S.C. §112, first paragraph. Accordingly, removal of the rejection is requested.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 15, 18-22 and 44-46 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 677-1456. Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

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